

# Pain Behavioral & Neural Responses to Pain

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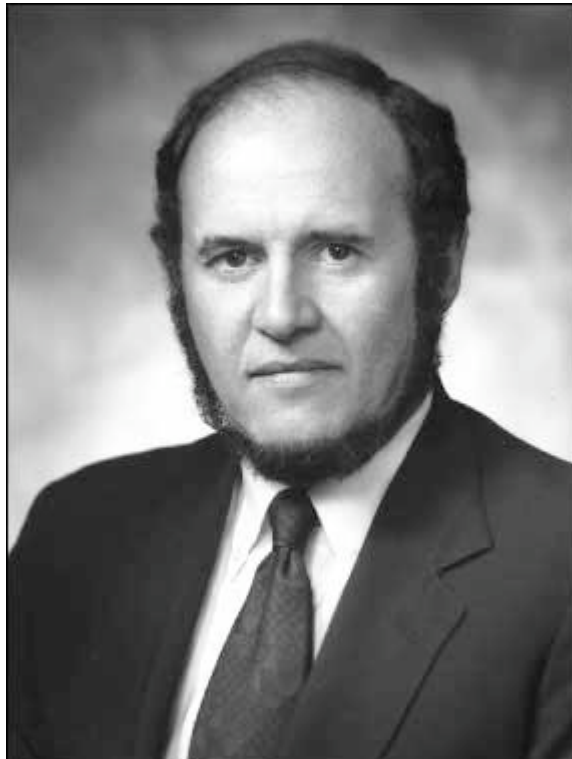
### The Monkey's Informed Choices

The awake behaving monkey experiments were among the most important undertaken by the Neurobiology and Anesthesiology Branch at NIDR in the 1970s and 1980s. These were real time observations of the ways in which an animal processed, reacted to, and acted on complex environmental information, including a noxious stimulus (a contact thermode placed near the lip), while microelectrode recordings were taken of the neuronal activity in the trigeminal brainstem. Originally designed by Ron Dubner and Ralph Beitel, the behavioral studies continued through several generations of postdocs and lab workers, including Catherine Bushnell, Gary Duncan, Ron Hayes, Donna Hoffman, Daniel Kenshalo, William Maixner, and Jean-Marie Oliveras .

Essential to the project were Fred Brown's skills and almost tactile sense of electronics, which enabled him to design and build the specifically configured equipment the researchers used to make very fine and precise real-time adjustments in stimulus intensity, timing, and duration.

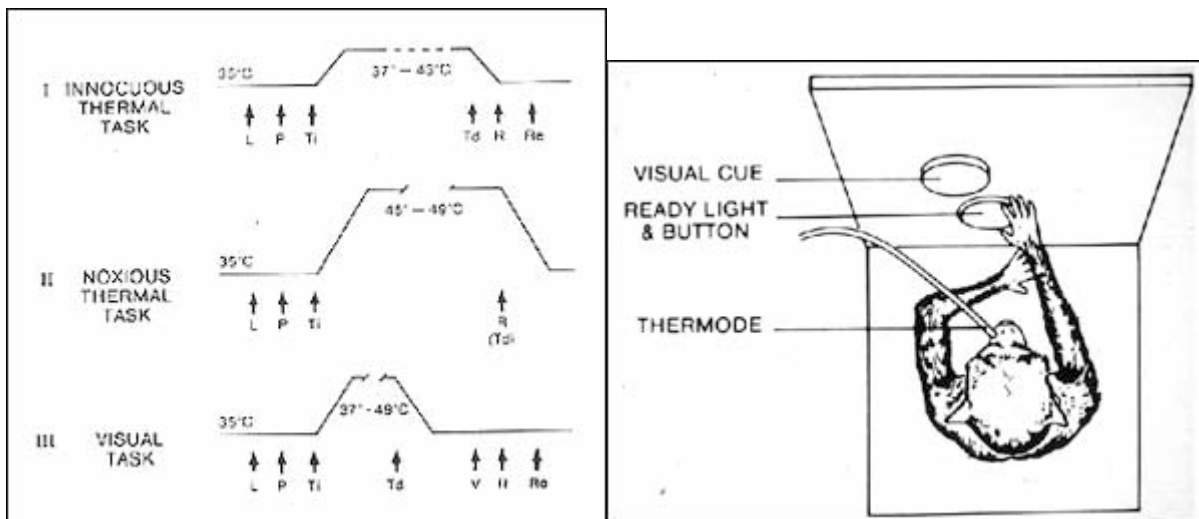
Ron Dubner described the monkey experiments: "You asked your questions through [the behavior]. Once you did that, and once you successfully recorded from neurons while the animal was performing the behavior, the data just fell out...The nervous system was telling you what it was doing."

- –Interview with Ron Dubner, 1999



Ronald Dubner, 1970s Photograph courtesy of NIDCR Public Information Office

Monkeys were trained in several complex tasks. In an initial task, the monkeys responded to a perceived shift in temperature, by pressing a panel to receive "a liquid reward" (water or juice). A second model allowed the monkey to make "informed choices" and forced him to discriminate between behaviorally-relevant and non-relevant stimuli.



From Task-related responses of monkey medullary dorsal horn neurons

The monkey could choose to initiate a trial at any time by pressing a panel and could terminate any painful stimulus by releasing the panel. When he activated the stimulus, the thermode presented sequences of low and high-temperature heat pulses in a "quasi-random" sequence. If the monkey released the panel within two seconds after he detected a temperature shift downward, he received his reward. Noxious stimuli (45 °C or higher) were presented for only a few seconds and could be immediately terminated by the monkey. He would receive no reward, however, unless he waited for the downward shift. A third type of task required the monkey to earn his reward by responding to a visual cue (light), while ignoring the temperature shifts of the thermode pulse (although again, noxious stimuli could be terminated immediately.)

Once a monkey had learned the tasks, the researchers began recording trigeminal neuron activity, using a microelectrode method developed by Ed Evarts at the National Institute of Mental Health (NIMH). The key data recorded were the time delay before the nerve responded to a stimulus and the frequency with which the nerve "fired". These were analyzed in conjunction with electrophysiological recordings from the same neurons in anesthetized animals and with anatomical and cytological observations under electron microscopy.



Apparatus built by Fred Brown to administer thermal stimuli and record nerve impulses

## Findings from the Behaving Monkey Studies

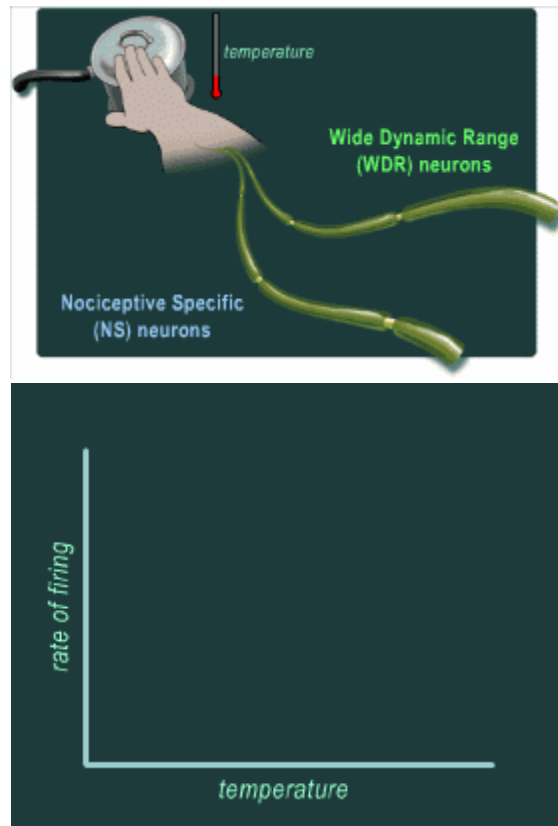
- "Wide-dynamic-range" neurons, not pain-specific cells, are most active in discriminations of changes in stimuli intensity
  - Behaviorally relevant stimuli trigger "a neuronal burst" of activity, independent of stimuli intensity
  - Detection of temperature shifts, in monkeys and humans, is an index of pain sensation
1. The physiological studies had identified two types of nociceptive neurons, neurons which responded to painful stimuli, in the trigeminal system and the spinal cord. "Nociceptive-specific" neurons responded with high levels of activity; but "wide-dynamic-range" (WDR) neurons responded with graded sensitivities, depending on the intensity of the stimulus. Even light touch applied to the center of the WDR neuron's receptive field would trigger a response, but stronger pressure was required in the surrounding area; and at the perimeter of the field, only a painful stimulus such as pinch would cause the neurons to fire.

Behavioral recordings from these different neurons during the awake behaving monkey studies showed that the WDR neurons, which were active at both innocuous and noxious stimulus levels, were those most involved in the monkey's perception of temperature shifts.

2. As the experimenters began offering well-trained monkeys more choices and decisions to make, they established that non-behaviorally significant stimuli -- an change in temperature that was irrelevant to the monkey's reward-seeking actions, for example -- led to only low levels of response from the WDR neurons. But light or heat stimuli important to the monkey's choices and behavior triggered very high, rapid levels of firing. These variations in nerve response were independent of the actual level of stimulus intensity. Thus, the nerve activity was the product of both sensory input and behavioral state.

These observations supported the concept of pain as dynamic and experiential: while the neurons involved in the monkey's behavior were highly specific in type and function, they were capable of different perceptual and behavioral responses to the same stimuli, depending on other environmental and internal events. This flexibility suggested that the nervous system is highly plastic and adaptive as an organism learns from and behaves within the outside environment.

3. In a subsequent series of experiments, Dan Kenshalo asked human volunteers to detect small shifts in painful stimuli and to estimate the intensity; correlation of "detection speed" with the monkeys' showed that "the monkeys and humans perceive, in terms of their detection speeds, about the same thing, and...they're all an index of the measure of pain sensation, pain intensity." –Interview with Daniel Kenshalo, Jr., 2000.



Both Nociceptive-Specific neurons and Wide-Dynamic-Range neurons increase their rates of firing as the intensity of the pain stimulus (the hot pot) increases. Wide-dynamic-range neurons, however, show an accelerated increase in firing rate; these neurons are the most sensitive to changes in stimulus intensity. Drawing and Graph by Donald Bliss.

Testing Old and New Drugs for Pain